

NEWS, VIEWS, AND REVIEWS

An Update on Common Genodermatoses Not to be Missed

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INTRODUCTION

Genodermatoses comprise a group of inherited disorders characterized primarily by cutaneous manifestations, encompassing over 1,000 conditions, and representing approximately 15% of all genetic disorders.[1] Among the most frequently encountered genodermatoses are filaggrin nonsyndromic epidermal differentiation disorder (FLG-nEDD), formerly known as ichthyosis vulgaris, neurofibromatosis type 1 (NF1), and epidermolysis bullosa (EB).[2,3] Genodermatoses impose a substantial psychosocial burden on affected children and their families.[4,5,6] The therapeutic landscape for several genodermatoses has evolved from supportive management to targeted approaches, including recent United States Food and Drug Administration (FDA) approvals for EB and promising investigational therapies for NF1. Although genodermatoses are rare, awareness of evolving therapies remains important, given the significant morbidity and associated quality-of-life (QOL) burden. As such, this review highlights advances in the classification and management of select genodermatoses that have undergone recent innovation.

Epidermolysis Bullosa

EB is a group of inherited blistering disorders with an estimated US prevalence of 11.07 per 1 million live births.[7] EB simplex (EBS) is the most common subtype, accounting for approximately 70% of cases, and results from mutations in genes encoding keratin 5 (KRT5) and keratin 14 (KRT14), which form keratin scaffolding within basal keratinocytes.[8] Dysfunction of these proteins compromises epidermal integrity, resulting in blister formation following minor friction or trauma.[8] Despite EBS being the most common subtype of EB, no FDA-approved treatments exist.[8] The current management remains largely supportive and focuses on minimizing weight-bearing on blister-prone surfaces, blister lancing, local wound care, treatment or prevention of skin infections, and balneotherapy, with evidence supporting dilute bleach baths, white vinegar soaks, and salt baths.[8] Many off-label therapies have been used in the management of EBS and are currently under investigation, including 2% topical sirolimus.[8] A phase II clinical trial (NCT02960997) assessing the use of topical sirolimus 2% in 16 EBS patients with plantar lesions found a decrease in EB disease activity and scarring index compared to placebo, though not statistically significant.[8] Additionally, deucravacitinib, an oral tyrosine kinase 2 (TYK2) inhibitor approved for the treatment of psoriasis at 6 mg once daily, is currently being investigated for EBS in an open-label phase II study (NCT06136403).[8]

Other subtypes of EB include dystrophic EB (DEB) and junctional EB (JEB).[8] Disease onset typically occurs at birth or in early infancy, with severe subtypes requiring intensive lifelong wound care.[9] Mortality remains high in severe JEB and recessive DEB (RDEB), with sepsis, respiratory failure, and malnutrition as major causes of early death.[9] In adults with RDEB, squamous cell carcinoma (SCC) is the leading cause of mortality.[9] Fortunately, the therapeutic landscape for EB has been transformed by three FDA-approved therapies within the past three years.[10,11,12]

Beremagene geperpavec (B-VEC), approved in 2023 as the first topical gene therapy for any disease, restores type VII collagen expression in DEB and significantly improves wound healing, as demonstrated in the phase III GEM-3 trial, with sustained efficacy and favorable long-term safety.[10] Birch triterpenes gel was approved in 2023 for the treatment of wounds associated with DEB and JEB, supported by findings from the phase III EASE trial demonstrating improved wound closure rates.[11] In 2025, prademagene zamikeracel became the first autologous ex vivo gene-corrected cell therapy for recessive DEB, demonstrating significant wound healing and pain reduction in the phase III VIITAL trial.[12]

In addition to updates in EB-related wound care, emerging evidence highlights a new potential therapy for cutaneous SCC (cSCC) in EB.[13] A patient with RDEB and multiple unresectable cSCCs achieved complete regression of several lesions and durable disease control for over a year after 10 cycles of pembrolizumab treatment (2 mg/kg every 3 weeks), an anti-programmed cell death protein 1 (PD-1) inhibitor, highlighting PD-1 blockade as a promising nonsurgical option.[13]

Neurofibromatosis type 1

NF1 is an autosomal dominant disorder characterized by café-au-lait macules (CALS), intertriginous freckling, multiple cutaneous neurofibromas (cNFs), Lisch nodules, distinctive osseous lesions, and learning disabilities.[14] NF1 affects approximately 1 in 3,000 births and is caused by loss-of-function mutations in the NF1 gene, which encodes neurofibromin, a negative regulator of RAS signaling.[3,14] Diagnosis requires the presence of at least two of the aforementioned clinical features, or one feature in an individual with an affected first-degree relative.[15] The 2021 revised diagnostic criteria include the identification of a pathogenic NF1 variant on genetic testing, an update particularly relevant in young children who may not yet manifest the clinical phenotype.[15]

cNFs develop in more than 95% of patients and can significantly impair QOL, particularly when located on visible areas such as the

face.[16] Despite this burden, FDA-approved therapies are lacking, and management remains procedural, including surgical excision, laser ablation, and electrodesiccation.[17] Emerging minimally invasive approaches may expand treatment options for cNFs, with a recent study highlighting the ability of a unique treatment modality, a 755-nm alexandrite laser with suction-assisted cooling, to selectively target cNF tissue while limiting injury to surrounding skin.[18]

NF1 may also be associated with plexiform neurofibromas (PNs), peripheral nerve sheath tumors that can cause substantial morbidity.[19] Two MEK inhibitors, selumetinib and mirdametinib, were approved by the FDA in 2020 and 2025, respectively, for patients with NF1-associated symptomatic, inoperable PNs, and this drug class is currently being investigated for the treatment of cNFs.[19-21] NFX-179, a topical MEK inhibitor, is a promising investigational therapy for cNFs.[22] In a phase 2a trial (n = 48), NFX-179 demonstrated a dose-dependent reduction in phosphorylated extracellular signal-related kinase, a biomarker of disease activity in cNFs, with a 47% decrease observed in the 0.5% treatment group at day 28 compared with vehicle (P=0.0001).[22] Additionally, 20% of cNFs treated with 0.5% NFX-179 achieved at least 50% volume reduction compared with 6% in the vehicle group (P=0.021), with no reported local or systemic toxicities.[22] If approved, NFX-179 would represent the first topical targeted therapy for cNFs, potentially shifting management from procedural to medical therapy.

Filaggrin Nonsyndromic Epidermal Differentiation Disorder

Recent advances in molecular genetics have prompted a shift in the classification and nomenclature of inherited ichthyoses. In 2025, experts proposed a gene-based classification system that redefined these conditions as epidermal differentiation disorders (EDDs), grouping them by the causative gene and underlying disease mechanism rather than by clinical morphology.[23] This framework improves diagnostic clarity and replaces potentially stigmatizing terminology. Under this nomenclature, ichthyosis vulgaris was renamed filaggrin nonsyndromic epidermal differentiation disorder (FLG-nEDD), reflecting its genetic basis in the filaggrin (FLG) gene.[23]

While EB and NF-1 have undergone recent therapeutic advances, the treatment paradigms for FLG-nEDD, the most common genodermatosis, with a prevalence ranging from 1:80 to 1:250, have remained largely unchanged.[24] FLG-nEDD results from mutations in FLG, a protein essential for epidermal barrier function, leading to generalized fine scaling, skin thickening, and compromised barrier function, and may be associated with pruritus and skin fragility.[23,25]

Management has remained consistent, including topical emollients, balneotherapy, keratolytics, topical retinoids, and systemic retinoids, such as acitretin, at doses ranging from 1mg/kg/day to 75 mg/day.[25] A 2025 review proposes a shift in future directions for therapy, including immunotherapeutic approaches targeting cytokines.[24] Evidence has demonstrated that T-helper (Th)2-mediated cytokines, particularly interleukin (IL)-4 and IL-13, suppress FLG expression and contribute to epidermal barrier dysfunction, supporting investigation of targeted biologic therapies such as dupilumab and tralokinumab in severe cases of FLG-nEDD, though no reports have directly studied this.[24]

CONCLUSION

Recent advances have transformed the therapeutic landscape of several genodermatoses, especially EB and NF-1. In EB, the emergence of gene-based therapies has shifted management from supportive wound care toward disease-modifying treatment. Similarly, investigational targeted pathway inhibitors in NF-1 represent a promising transition from procedural to precision management. Although treatment of FLG-nEDD remains largely supportive, increasing understanding of immune dysregulation and Th2-mediated suppression of filaggrin expression has led to growing interest in targeted immune modulation. Together, these advances highlight a broader shift toward mechanism-based therapies that may significantly improve outcomes and QOL for patients with genodermatoses.

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